Study Protocol

Title: "*Phase II/III Clinical Trial study to evaluate efficacy and Safety of C-IVIG therapy in Severe COVID-19 Patients".*

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STUDY PROTOCOL

General Information:

Title: "*Phase II/III Clinical Trial study to evaluate efficacy and Safety of C-IVIG therapy in Severe COVID-19 Patients".*

Principal and Co-Prinicipal Investigators

Principal Investigator: Dr. Shaukat Ali

Co- Principal Investigator: Dr. Shobha Luxmi

Co- Principal Investigator: Abdul Samad Khan

Co-Principal Investigator: Dr. Muneeba Ahsan Sayeed

Trial Sites

Dow University of Health Sciences (Ojha Campus), Karachi, Sindh

Sindh Infectious Disease Hospital and Research Center, Karachi, Sindh

PAF hospital Faisal Base, Karachi, Sindh

Background Information:

Anti-COVID19 Intravenous immunoglobulin (C-IVIg) is a mixture of IgG, IgA, IgM and Albumin derived from recovered COVID1-19 participant via Caprylic acid process. Anti-COVID19 Intravenous immunoglobulin (C-IVIg) Contain a total amount of protein 46±3.7g/L in which upto 80% is IgG, 4.0% is IgM, IgA is 15.8% and Albumin is <0.4. Anti-COVID19 C-IVIG is used in the treatment COVID 19 severe and critical patients. The dosage form is Liquid and route of administration is intravenous. The indication to given C-IVIG is PCR positive COVID 19. In non-clinical studies C-IVIG has been observed Safety and in phase I trial shown remarkable results in Safety as well as efficacy at Dow University Hospital, Karachi. 28 day mortality have been reduced markedly which were given single dose of C-IVIG intravenously with Standard of Care when compared to Control with Standard of care. It has been observe that in 28 day patient monitoring did not report any drug related serious adverse event like organ damage, disability or permanent damage.

Objective

The aim of this trial is to investigate the safety and clinical efficacy of passive immunization therapy through Hyperimmune anti-COVID-19 Intravenous Immunoglobulin (C-IVIG: 5% liquid formulation), on severe COVID-19 patients.

Trial Design

This is a phase II/III multi-centred, randomized controlled, single-blinded, superiority trial, through parallel-group design. Participants will be randomized either to receive C-IVIG and standard care or placebo and standard care (1:1).

Participants

Consenting patients above 18 years that are classified by the treating physician as severe i.e. showing symptoms of COVID-19 pneumonia, dyspnea, respiratory rate ≥30/min, blood oxygen saturation ≤90%, PaO_2/FiO_2 <300, and lung infiltrates as seen on CXR/HRCT> 50% (on ≤15 Liters supplemental oxygen).

Critical COVID-19 patients (patients requiring mechanical ventilation) and patients given immunomodulatory drug (Tociluzumab) are excluded from study. Patients with reported IgA deficiency, autoimmune disorder, thromboembolic disorder, and allergic reaction to immunoglobulin treatment were excluded from study. Similarly, pregnant females, patients requiring two or more inotropic agents to maintain blood pressure and patients with chronic kidney injury/failure, were also excluded from the study.

Intervention and comparator

The study consists of intervention comprising of two groups with each group containing 155 participants. All participants will receive standard hospital care which includes airway support, anti-viral medication, antibiotics, fluid resuscitation, hemodynamic support, steroids, painkillers, and anti-pyretic. Randomized test patients will receive single dose of C-IVIG in following two dosage groups:

Group 1 (Test): Severe COVID-19 patients: Single dose of 0.15g/Kg with standard hospital care

Group 2 (Comparator): Severe COVID-19 patients: placebo with standard hospital care

Selection and Withdrawal of Subjects

Plasma collection from donors (recovered COVID-19 individuals):

Selection of donor according to World Health Organization (WHO) and Federal Drug Agency (FDA) guidelines

Inclusion Criteria for Donor	***Exclusion criteria for Donor***
a. Submitted signed consent. b. Eligible to donate blood. c. Negative for HIV, HBV, HCV, syphilis and malarial parasite. d. Complete resolution of symptoms at least 14 e. days prior to donation f. Defined SARS-CoV-2 neutralizing antibody activity	a. Pre-existing condition Contra indicative for donating blood (HIV, viral hepatitis, tuberculosis, syphilis, oncological conditions, malaria). b. Bleeding tendency. c. Anemia. d. Fever of unknown origin

Plasma Collection

300-1000 ml plasma will be collected from consenting COVID-19 recovered patients (two weeks after resolution of symptoms) using plasmapheresis technique. Plasmapheresis is a technique where using a machine the blood components are separated, keeping the required component, in this case plasma, and returning other components like RBCs. Plasma will be stored according

to WHO guidelines. Aliquot of plasma will be screened for syphilis, malarial parasite HIV, HBV, HCV, and COVID–19 by Nucleic Acid Test (NAT). The screened stored plasma qualifying safety criteria will be pooled and fractionated to obtain Anti-COVID hyperimmune immunoglobulin.

Administration of C-IVIG in respective doses by medical experts in selected recipient

Recipient criteria

Inclusion criteria for Recipient	***Exclusion criteria for Recipient***
1. Above 18 years of age 2. Have positive COVID PCR on nasopharyngeal and/or oropharyngeal swabs 3. classified as severe* COVID-19 according to WHO guideline 4. Consent given by the patient or first degree relative	a. Critical COVID-19 patients b. Pregnant females c. Previous allergic reaction to immunoglobulin treatment d. Patient given immunomodulatory drug (e.g. tociluzumab) e. Patient requiring 2 inotropic agents to maintain blood pressures f. Known case of any autoimmune disorder g. Chronic kidney disease h. Known case of thromboembolic disorder i. Aseptic meningitis

*Severe COVID-19 is defined by one or more of the following: dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤90%, PaO_2/FiO_2 ratio <300, lung infiltrates as seen through CXR/HRCT >50% (On ≤15 Liters supplemental oxygen)